

Impact of Rituximab on COVID-19 in Immunocompromised Patients: A Nationwide Cohort Study in Korea

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Background. Anti-CD20 therapy has been associated with severe pneumonia in coronavirus disease 2019 (COVID-19) patients. This study aimed to evaluate the impact of anti-CD20 therapy on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19-related outcomes using a nationwide cohort.

Methods. We used the K-CoV-N database, integrating the Korea Disease Control and Prevention Agency and the National Health Insurance Service. Adults (≥ 19 years) diagnosed with conditions warranting anti-CD20 therapy from January 2020 to December 2021 were included. Patients initiating rituximab (RTX) during the study period were defined as RTX users, whereas RTX nonusers were selected through propensity score matching. Logistic regression analyses were used to estimate the association between RTX use and SARS-CoV-2 infection, as well as COVID-19-related outcomes.

Results. Among 1 548 038 patients requiring anti-CD20 therapy, 1 457 171 were vaccinated and 90 867 were unvaccinated. In the vaccinated group, RTX use was not significantly associated with an increased risk of SARS-CoV-2 infection (adjusted odds ratio [aOR] 1.75; 95% confidence interval [CI], .82–3.72; $P = .149$) but was linked to higher hospitalization for COVID-19 (aOR 2.64; 95% CI, 1.14–6.10; $P = .024$) and intensive care unit admission (aOR 10.89; 95% CI, 1.44–82.46; $P = .021$). In the unvaccinated group, RTX use showed no statistically significant associations with severe COVID-19 outcomes.

Conclusions. Using a nationwide dataset, this study found that RTX use is associated with an increased risk of severe COVID-19 outcomes in vaccinated individuals. Despite rising vaccination rates, clinicians should carefully weigh the risks and benefits of anti-CD20 therapy during the COVID-19 pandemic.

Keywords. anti-CD20 therapy; COVID-19; rituximab; SARS-CoV-2.

Immunocompromised patients receiving anti-CD20 therapy, such as rituximab (RTX), have shown increased risk of severe outcomes during the coronavirus disease 2019 (COVID-19) pandemic, including pneumonia and prolonged viral shedding. Several observational studies have reported prolonged viral shedding and higher mortality rates in COVID-19

patients treated with RTX, particularly among patients with hematologic malignancies [1, 2]. However, these findings are limited by small sample sizes and their focus on specific populations. The broader impact of RTX therapy on COVID-19 outcomes across diverse populations remains unclear, particularly after the widespread use of vaccination. Additionally, the effect of COVID-19 vaccination in patients treated with RTX is not clearly elucidated, although the protective effect of vaccination is well established [3].

This study aimed to evaluate the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe COVID-19 outcomes in patients with similar underlying conditions by comparing RTX users and nonusers using a nationwide big data cohort. The K-CoV-N dataset integrated data from the Korea Disease Control and Prevention Agency (KDCA) registry dataset and the National Health Insurance Service (NHIS). All confirmed COVID-19 cases in Korea were reported to the KDCA through mandatory reporting systems, ensuring comprehensive and reliable case identification. Additionally, NHIS, as Korea's single-payer healthcare system, provides detailed patients' medical histories, including

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prescription drug use. These unique features allowed for a robust evaluation of RTX therapy's impact on COVID-19 outcomes while accounting for potential confounders, such as vaccination status and underlying comorbidities.

METHODS

Data Source and Study Population

This retrospective cohort study utilized the K-COV-N cohort, developed by the KDCA and the NHIS [4, 5]. This cohort integrates COVID-19 registry data from the KDCA with claims data from the NHIS, providing a comprehensive nationwide resource. It includes diagnoses, procedures, health check-ups, prescription records, COVID-19 vaccination status, and SARS-CoV-2 test results. All data were anonymized in accordance with confidentiality guidelines to protect patient privacy.

This study analyzed data from January 2015 to December 2021 and included adult patients (≥ 19 years) diagnosed with conditions potentially requiring immunosuppressant use, such as lymphoma, leukemia, rheumatoid arthritis, or kidney transplantation, or those patients prescribed immunosuppressive medications between January 2020 and December 2021. Detailed lists of included conditions and medications are provided in [Supplementary Tables 1 and 2](#).

Definitions of Exposure and Outcomes

RTX use was defined as the first prescription of RTX during the study period, from January 2020 to December 2021. Patients who did not receive RTX prescription during this period were classified as RTX nonusers. The index date was defined as the date of the first RTX prescription after January 2020 for RTX users and as the date of the first occurrence of a relevant diagnostic code for RTX nonusers.

The primary outcome was the incidence of confirmed SARS-CoV-2 infection occurring after the index date during the study period. Secondary outcomes included hospitalization, intensive care unit (ICU) admission, and the use of mechanical ventilation within 30 days of a COVID-19 diagnosis, serving as proxies for disease severity. Outcomes were analyzed only if they occurred after the initial use of RTX or other immunosuppressive medications, or the appearance of relevant diagnostic codes.

Covariates

Sociodemographic data, including age, sex, and insurance type (health insurance or medical aid) were collected. Comorbidities were identified from diagnostic records within 5 years preceding the index date, focusing on clinically relevant conditions recorded at least 3 times. These conditions were categorized into 7 morbidity groups: hematologic malignancies, benign hematologic disorders, other malignancies, rheumatic diseases,

neurologic diseases, kidney diseases, and others. To evaluate patients' disease severity, we further stratified them into 3 severity groups based on the number of comorbidities as a proxy indicator: no comorbidity, 1 comorbidity, and 2 or more comorbidities. A detailed list of comorbidity categories is provided in [Supplementary Table 3](#).

COVID-19 vaccination records were also collected. Patients with no recorded vaccination during the study period were classified as the unvaccinated group. Those who received their first dose before the occurrence of an outcome (confirmed COVID-19 case) were classified as the vaccinated group; those whose first dose was administered after the occurrence of the outcome were classified as the unvaccinated group.

Statistical Analysis

Propensity score (PS) matching was applied to control for covariate imbalance and minimize treatment assignment bias. RTX users were matched to nonusers in a 1:10 ratio for the vaccinated group and a 1:5 ratio for the unvaccinated group using the greedy matching method. The caliper width was set to 0.2 of the pooled standard deviation of the logit of the PS [6]. Matching variables included age groups (20s, 30s, 40s, 50s, 60s, 70s, 80+ years), sex, insurance type, and comorbid conditions. The balance of matching was assessed using the standardized mean difference, with values less than 0.1 indicating good balance.

Demographic and clinical characteristics were summarized as frequencies and percentages for categorical variables and as means with standard deviations for continuous variables. The associations between RTX use and outcomes was evaluated using univariate and multivariable logistic regression models with results presented as odds ratios with 95% confidence intervals (CIs). To assess the effect of RTX on COVID-19 severity, additional logistic regression analyses were conducted within the subgroup of confirmed COVID-19 cases. All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, North Carolina, United States).

RESULTS

Study Population and Baseline Characteristics

A total of 1 548 038 patients diagnosed with conditions potentially requiring immunosuppressant use or prescribed immunosuppress medications were included in the study. Among these, 1 457 171 were vaccinated and 90 867 were unvaccinated. Of the vaccinated patients, 645 were RTX users and 1 456 526 were RTX nonusers. In the unvaccinated patients, 286 were RTX users and 90 581 were RTX nonusers. After PS matching, 645 RTX users were matched to 6450 RTX nonusers in the vaccinated group (1:10 ratio), and 286 RTX users were matched to

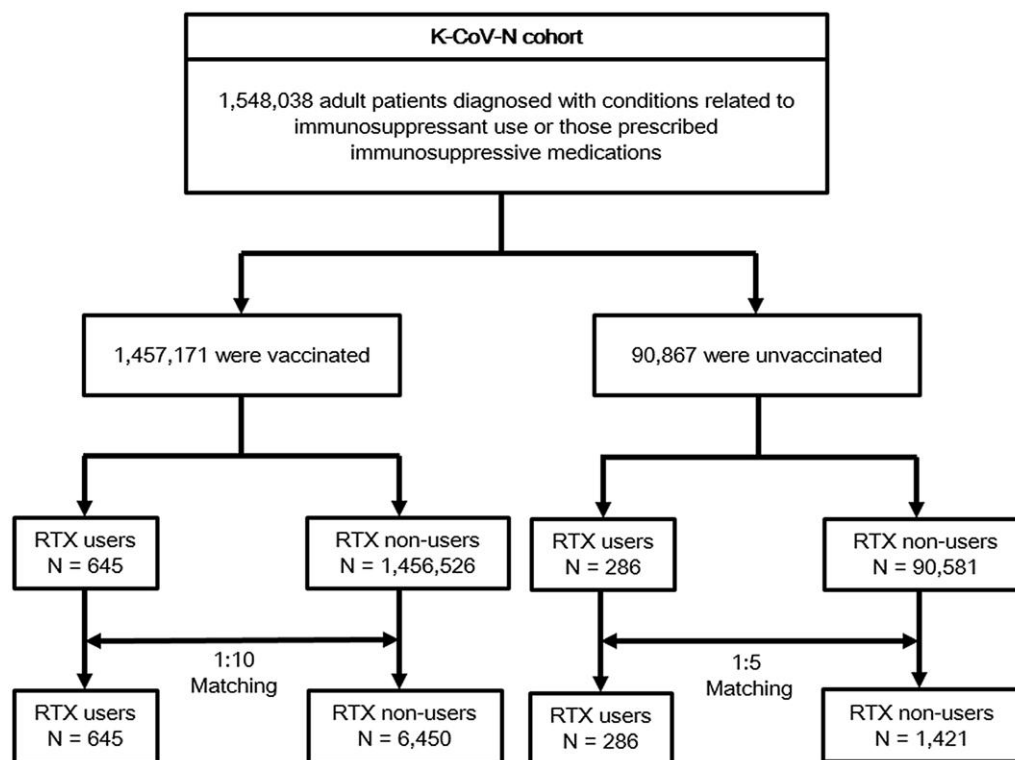


Figure 1. Flowchart of study population selection. RTX, rituximab.

1421 RTX nonusers in the unvaccinated group (1:5 ratio) (Figure 1).

Baseline characteristics of PS-matched RTX users and non-users in the vaccinated and unvaccinated groups are presented in Table 1. Among all RTX users included in the study, 54.7% of vaccinated patients and 58.4% of unvaccinated patients were aged 60 years or older. Hematologic malignancies were the most common comorbidities, observed in 56.0% of vaccinated patients and 58.0% of unvaccinated patients. Among RTX users, the cumulative numbers of RTX administrations from the first dose to the last follow-up did not show a statistically significant difference between the vaccinated and unvaccinated groups (median [interquartile range (IQR)], 7 [3–12] versus 6 [2–12], $P = .305$). However, the vaccinated group had a significantly longer RTX treatment duration compared to the unvaccinated group (median [IQR], days: 106 [19–134] vs 84 [14–126], $P = .015$). Among 645 RTX users in the vaccinated group, 417 patients had received RTX only before COVID-19 vaccination, with a median interval of 261 days (IQR 136–396) between last RTX and COVID-19 vaccination. For the 228 patients who received RTX after COVID-19 vaccination, the median interval between COVID-19 vaccination and subsequent RTX administration was 28 days (IQR 14–59.5). After PS matching, all absolute standardized mean difference values for covariates were below 0.1, indicating

successful balance between RTX users and nonusers (Supplementary Figs. 1 and 2).

Association Between Rituximab Exposure and Incidence and Outcomes of COVID-19

In the vaccinated group, RTX exposure was not significantly associated with SARS-CoV-2 infection (adjusted odds ratio [aOR], 1.75; 95% CI, .82–3.72; $P = .149$). However, RTX exposure was significantly associated with higher odds of hospitalization (aOR, 2.64; 95% CI, 1.14–6.10; $P = .024$), ICU admission (aOR, 10.89; 95% CI, 1.44–82.46; $P = .021$), and mechanical ventilator administration (aOR, 10.89; 95% CI, 1.44–82.46; $P = .021$, Table 2).

In the unvaccinated group, RTX exposure was associated with a reduced risk of confirmed COVID-19 (aOR, 0.32; 95% CI, .13–.81; $P = .017$). However, no significant effects were observed on hospitalization (aOR, 0.42; 95% CI, .15–1.15; $P = .098$), ICU admission (aOR, 0.51; 95% CI, .06–4.13; $P = .528$), and mechanical ventilator administration (aOR, 0.84; 95% CI, .10–7.31; $P = .878$, Table 3).

In an additional analysis adjusting for comorbidity burden, using the number of coexisting conditions as a proxy for disease severity, the association between RTX use and an increased risk of severe COVID-19 outcomes—including hospitalization, ICU admission, and mechanical ventilation—remained statistically

Table 1. Baseline Characteristics of RTX Users and Nonusers After Propensity Score Matching

| Variables | Vaccinated (n = 7095) | | | | Unvaccinated (n = 1707) | | | |
|------------------------------|-----------------------|------|---------------------------|------|-------------------------|------|---------------------------|------|
| | RTX User (n = 645) | | RTX Nonuser (n = 6450) | | RTX User (n = 286) | | RTX Nonuser (n = 1421) | |
| | N | % | N | % | N | % | N | % |
| Sex | | | | | | | | |
| Male | 342 | 53.0 | 3327 | 51.6 | 142 | 49.7 | 702 | 49.4 |
| Female | 303 | 47.0 | 3123 | 48.4 | 144 | 50.3 | 719 | 50.6 |
| Age, y | | | | | | | | |
| 20–30 | 19 | 3.0 | 198 | 3.1 | 11 | 3.9 | 53 | 3.7 |
| 30–40 | 38 | 5.9 | 355 | 5.5 | 26 | 9.1 | 130 | 9.2 |
| 40–50 | 90 | 14.0 | 904 | 14.0 | 35 | 12.2 | 166 | 11.7 |
| 50–60 | 145 | 22.5 | 1471 | 22.8 | 47 | 16.4 | 213 | 15.0 |
| 60–70 | 181 | 28.1 | 1777 | 27.6 | 65 | 22.7 | 366 | 25.8 |
| 70–80 | 128 | 19.8 | 1316 | 20.4 | 52 | 18.2 | 257 | 18.1 |
| ≥80 | 44 | 6.8 | 429 | 6.7 | 50 | 17.5 | 236 | 16.6 |
| Insurance type | | | | | | | | |
| Health insurance | 611 | 94.7 | 6123 | 94.9 | 268 | 93.7 | 1331 | 93.7 |
| Medical aid | 34 | 5.3 | 327 | 5.1 | 18 | 6.3 | 90 | 6.3 |
| Comorbidities | | | | | | | | |
| Hematologic malignancies | 361 | 56.0 | 3610 | 56.0 | 166 | 58.0 | 821 | 57.8 |
| Benign hematologic disorders | 23 | 3.6 | 216 | 3.4 | 9 | 3.2 | 38 | 2.7 |
| Other malignancies | 102 | 15.8 | 1049 | 16.3 | 37 | 12.9 | 199 | 14.0 |
| Rheumatic diseases | 138 | 21.4 | 1425 | 22.1 | 61 | 21.3 | 299 | 21.0 |
| Neurologic diseases | 65 | 10.1 | 627 | 9.7 | 37 | 12.9 | 188 | 13.2 |
| Kidney diseases | 43 | 6.7 | 428 | 6.6 | 22 | 7.7 | 125 | 8.8 |
| Others | 101 | 15.7 | 1055 | 16.4 | 48 | 16.8 | 273 | 19.2 |

Values are presented as number and percent.

Abbreviation: RTX, rituximab.

Table 2. Association Between RTX Exposure and COVID-19–related Outcomes in the Vaccinated Group

| Outcomes | OR (95% CI) | P | aOR (95% CI) | P |
|----------------------------------------------|--------------------|------|--------------------|------|
| COVID-19 (n = 54) | 1.75 (.82–3.72) | .150 | 1.75 (.82–3.72) | .149 |
| Hospitalization (n = 34) | 2.61 (1.13–6.02) | .031 | 2.64 (1.14–6.10) | .024 |
| ICU admission (n = 4) | 10.03 (1.41–71.31) | .044 | 10.89 (1.44–82.46) | .021 |
| Mechanical ventilator administration (n = 4) | 10.03 (1.41–71.31) | .044 | 10.89 (1.44–82.46) | .021 |

Multivariable analyses adjusted for sex, age, insurance type, and comorbidities.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit; OR, odds ratio; RTX, rituximab.

significant in the vaccinated group but not in the unvaccinated group ([Supplementary Table 4](#)).

After adjusting for other immunosuppressive agents, including corticosteroids, interleukin-6 inhibitors, Janus kinase inhibitors, abatacept, and tumor necrosis factor- α inhibitors, RTX use remained significantly associated with an increased risk of hospitalization, ICU admission, and mechanical ventilator administration in the vaccinated group, but not in the unvaccinated group ([Supplementary Table 5](#)).

RTX Use in Subgroup of Confirmed COVID-19 Cases

Of the study population, 54 vaccinated and 77 unvaccinated patients were confirmed for SARS-CoV-2 infection. Detailed baseline characteristics of this subgroup are presented in

[Supplementary Table 6](#). Among the 54 vaccinated COVID-19 patients, 8 were RTX users. The median cumulative number of RTX administrations prior to COVID-19 diagnosis was 3.5 (IQR, 1.5–10.5), and the median duration from last RTX administration to COVID-19 diagnosis was 86 days (IQR, 53.5–311). Among the 77 unvaccinated COVID-19 patients, 5 were RTX users. The median cumulative number of RTX administration prior to COVID-19 diagnosis was 4.0 (IQR, 2.0–4.0), and the median duration from last RTX administration to COVID-19 diagnosis was 165 days (IQR, 97–606).

DISCUSSION

Although the World Health Organization declared the end of the COVID-19 pandemic in May 2023, the risk of severe

Table 3. Association Between RTX Exposure and COVID-19–related Outcomes in the Unvaccinated Group

| Outcomes | OR (95% CI) | P | AOR (95% CI) | P |
|----------------------------------------------|----------------|------|----------------|------|
| COVID-19 (n = 77) | .33 (.13–.83) | .014 | .32 (.13–.81) | .017 |
| Hospitalization (n = 49) | .43 (.15–1.22) | .102 | .42 (.15–1.15) | .098 |
| ICU admission (n = 10) | .55 (.07–4.36) | .322 | .51 (.06–4.13) | .528 |
| Mechanical ventilator administration (n = 7) | .83 (.10–6.90) | .391 | .84 (.10–7.31) | .878 |

Multivariable analyses adjusted for sex, age, insurance type, and comorbidities.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; ICU, intensive care unit; OR, odds ratio; RTX, rituximab.

COVID-19 remains, particularly for immunocompromised individuals, as new variants of SARS-CoV-2 continues to emerge. This study, using the nationwide K-CoV-N cohort, demonstrated that RTX exposure is significantly associated with poor COVID-19 outcomes, including hospitalization, ICU admission, and mechanical ventilator administration among vaccinated immunocompromised individuals. Importantly, these associations persisted even after adjusting for age and underlying comorbidities, emphasizing the independent effect of RTX on COVID-19 severity. These findings highlighted the need for caution when using RTX, even in the setting with high vaccination rates and comprehensive management of underlying diseases.

The association between RTX use and severe COVID-19 outcomes observed in this study aligns with previous research across various populations. A cohort study found that RTX use in patients with inflammatory rheumatic diseases is associated with severe COVID-19 and prolonged hospitalization [7]. Another study identified RTX maintenance therapy as a risk factor for COVID-19 pneumonia in patients with lymphoma [8]. Furthermore, anti-CD20 therapy has been implicated as a risk factor for death in COVID-19 patients with non-Hodgkin lymphoma [2]. Our previous research also found that B-cell depletion therapy was associated with severe to critical COVID-19 when comparing patients receiving B-cell depletion therapy and those with same underlying diseases who did not receive B-cell depletion therapy [9].

Following the rollout of the COVID-19 vaccine, concerns have emerged regarding vaccine-induced immune responses in patients undergoing B-cell depletion therapy. RTX-treated patients have shown impaired humoral immune responses to COVID-19 vaccination across various conditions. For instance, in patients with rheumatic diseases, only 39% of RTX-treated individuals demonstrated seropositive responses [10]. Lymphoma patients treated with RTX exhibited weaker humoral immune responses to COVID-19 mRNA vaccines compared to healthy controls [11]. The reduced immunogenicity might contribute to the poor COVID-related outcomes observed in RTX-treated vaccinated individuals in this study.

Vaccinated RTX users should be prioritized for additional preventive measures, such as social distancing and prophylactic monoclonal antibodies.

RTX is well-established as a crucial in managing B-cell lymphoproliferative diseases and refractory rheumatic diseases, but its association with infectious complications has long been recognized [12, 13]. Considering the heightened risk of severe COVID-19 outcomes, clinicians should carefully balance the benefit of RTX against its risks, especially during COVID-19 high-transmission periods. Alternative immunosuppressive therapies may be considered in cases where clinical efficacy is comparable. A study investigating the impact of long-term immunosuppressive medication use on in-hospital outcomes for patients with COVID-19 shown that, with the exception of rituximab, individuals receiving long-term immunosuppressive treatments who were hospitalized for COVID-19 did not have an increased risk of requiring invasive mechanical ventilation or experiencing in-hospital death [14]. Such alternatives could provide safer options for managing underlying conditions during ongoing COVID-19 risks.

In unvaccinated patients, the observed reduction in the risk of SARS-CoV-2 infection among RTX users, coupled with the lack of a significant association between RTX exposure and severe COVID-19 outcomes, represented an intriguing finding. This contrasts with the well-documented immunosuppressive effects of anti-CD20 therapy [15, 16], which are typically associated with an increased susceptibility to infections. Although COVID-19 vaccination has been widely recommended, vaccine uptake among patients with hematologic malignancies and other immunocompromised conditions remain suboptimal. Cross-sectional studies conducted in Korea and the United States have reported lower vaccination rates and higher vaccine hesitancy among immunocompromised individuals, including those with cancer and rheumatic diseases [17, 18]. Vaccine hesitancy in these population often arises from concerns about vaccine safety, particularly due to distrust in the rapid development process, especially among populations with lower educational and income levels [18, 19].

One possible explanation for these observations is that RTX users in the unvaccinated group may have adopted more cautious preventive behaviors, such as strict adherence to mask-wearing, physical distancing, and minimizing social interactions. Studies have shown that heightened fear of illness can improve compliance with preventive measures [20, 21]. Among RTX users, the decision to avoid vaccination, combined with fears of severe COVID-19 outcomes due to immunosuppressive therapy, may have heightened their awareness of infection risks and led to stricter adherence to infection control guidelines. A survey exploring the impact of COVID-19 vaccine on preventive measures found that the preventive behavior changed before and after completing COVID-19 vaccination. There was an increase in the percentage of respondents who

ate at a restaurant, used public transport, and attended indoor public places, whereas the percentage of those maintaining physical distancing decreased [22]. Additionally, differences in healthcare access may also explain these findings. RTX users, who require frequent visits for treatment and monitoring, may benefit from earlier detection and management of infections, potentially mitigating severe COVID-19 outcomes even without vaccination.

This study has several strengths. It utilized a comprehensive nationwide dataset with detailed medical histories and robust PS matching, minimizing confounding biases. However, there are several limitations. First, the study period predates the Omicron-dominant period, and the findings may not fully generalize to more recent periods dominated by the Omicron variants. Second, the number of confirmed COVID-19 cases was relatively small, limiting the statistical power in subgroup analyses. Third, the K-CoV-N cohort did not include clinical variables, such as body mass index and laboratory abnormalities and the severity of underlying comorbidities that could impact the severity of COVID-19. Fourth, differences in infection prevention behaviors between vaccinated and unvaccinated individuals could not be accounted for, as such information is not available in claims data. The potential influence of these behavioral factors on the observed differences between groups could have affected the results. Fifth, antiviral treatments for COVID-19, such as remdesivir or nirmatrelvir/ritonavir, were not included as covariates in the analysis. The use of these therapies may have influenced the severity of COVID-19 outcomes, particularly in immunocompromised patients. Despite these limitations, this study provides important insights into the risks associated with RTX use.

Using nationwide data, this study demonstrated that RTX exposure was associated with poor COVID-19-related outcomes, including hospitalization, ICU admission, and mechanical ventilator administration, in vaccinated immunocompromised individuals. Despite increased vaccination rates, physicians should carefully weigh the risks of poor COVID-19 outcomes against the therapeutic benefits of RTX. Preventive strategies, such as optimizing vaccination and exploring alternative therapies, should be prioritized to mitigate risks in RTX-treated individuals.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. P.G.C. and S.Y.K. conceived and designed the project. C.M.L., S.H.K., H.J.J., C.K.K., W.B.P., and N.J.K. analyzed the data. C.M.L. wrote the original draft with the help of all authors. P.G.C. and S.Y.K. took responsibility for the integrity of the data and the manuscript. The authors read and approved the final manuscript.

Availability of data and materials. Correspondence and requests for data should be addressed to S.Y.K. or P.G.C.

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Ethics approval. This study utilized a publicly available anonymized dataset, the K-CoV-N cohort, provided by the KDCA and NHIS. As the dataset contained no identifiable personal information and was publicly accessible, the study was exempted from review by the institutional review board of the Seoul National University Hospital (No. 2206-128-1335).

Potential conflicts of interest. All authors: No reported conflicts.

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